

# Neoadjuvant chemotherapy for muscle-invasive bladder cancer: Underused across the 49<sup>th</sup> parallel

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Despite local control with surgery or radiation, more than 50% of patients with muscle-invasive bladder cancer (MIBC) will relapse and die from distant metastases.<sup>1</sup> Micrometastatic deposits, present at the time of diagnosis but smaller than the detection threshold of modern imaging, are believed to be responsible for these relapses. Perioperative chemotherapy can eradicate these micrometastases.

In the neoadjuvant setting, randomized controlled trials<sup>2,3</sup> have consistently shown that cisplatin-based multi-agent chemotherapy prior to surgery improves overall survival by 5–10%. These results are supported by three subsequent meta-analyses, the most recent of which included 3285 patients from 15 randomized trials.<sup>4–6</sup> There is less Level 1 evidence to support the use of adjuvant chemotherapy (ACT). Three recent randomized trials have closed early due to poor accrual;<sup>7–9</sup> however, meta-analyses of these trials,<sup>10,11</sup> together with evidence from population-based studies,<sup>1</sup> suggest that ACT is associated with a survival benefit that is comparable to neoadjuvant chemotherapy (NAC).<sup>12</sup> On the basis of this cumulative evidence, cisplatin-based perioperative chemotherapy is the standard of care for MIBC.<sup>13–15</sup>

Despite its established survival benefit, uptake of perioperative chemotherapy for MIBC has been low and slow. Our group has previously described temporal trends in practice within the Canadian province of Ontario. In 2009, (10 years after the initial MRC trial was published showing an improvement in survival with NAC) the NAC utilization rate in Ontario was only 19%; by 2013, this had increased to 27%.<sup>16</sup> The rise in the use of NAC was concurrent with a rise in the proportion of patients who were referred to see a medical oncologist (MO) prior to cystectomy (21% in 2009 to 44% in 2013). The proportion of patients who saw a MO who were ultimately treated with NAC also increased substantially (32% in the period 1994–1998 to 54% in 2009–

2013). These findings suggest that increased use of NAC was driven by both increased referral rates from urology to MO and by greater use of chemotherapy by MO among referred patients. Rates of ACT utilization in Ontario remained relatively stable over time (15–22% from 1994–2013).

In the article that accompanies this editorial, Duplisea et al describe practice patterns in the U.S. Using the National Cancer Database (NCDB), they identified 18 188 patients undergoing radical cystectomy or partial cystectomy for clinical T2–T4N0M0 MIBC from 2006–2014. Overall, 3940 (22%) patients received NAC. Patients who did not receive NAC were older, had higher comorbidity scores, less insurance, lower income level, were treated at “lower-volume” radical cystectomy hospitals (<20 procedures per year), and were treated at non-academic facilities. Among those undergoing radical cystectomy, use of NAC increased from 10% in 2006 to 32% in 2014. The study authors were not able to comment on potential reasons for the low use of NAC and did not report on the proportion of patients who were referred to a MO, nor trends in the use of ACT.

The readership of *CUAJ* will note the striking similarity in practice between the U.S. and Canada (Table 1). As Canadians, our universal healthcare system is a collective point of national pride.<sup>17</sup> This sentiment can contribute to an illusion among some Canadian physicians and policy-makers that universal healthcare means universal access to the standard of care. Yet, there is compelling data to show that despite universal healthcare, there are important differences in Canadian cancer survival rates across social strata that may be directly attributable to access to therapy and quality of care.<sup>18</sup> Even among the socially advantaged, the study by Duplisea et al and our data in Ontario<sup>19</sup> show that the utilization rates of NAC are unacceptably low.

Why does practice lag behind evidence? It is not because urologists lack knowledge of the benefit of NAC. In a 2016 survey sent to all Canadian urologists who treat bladder cancer, among 110 respondents, the mean reported survival benefit associated with NAC was spot on at 9%.<sup>20</sup> Even among this highly selected group of urologists (90% stated

**Table 1. Use of neoadjuvant (NACT) and adjuvant (ACT) chemotherapy for muscle-invasive bladder cancer in the U.S. and Canada**

Partial cystectomy data	Duplisea et al (CUAJ 2018)	Booth et al (CUAJ 2017)
Years	2006–2014	1994–2008
Location	U.S.	Ontario, Canada
% of patients undergoing partial cystectomy	(1031/1888) 6%	(181/3320) 5%
NACT	10% (106/1031)	1% (<6/181)
ACT	Not reported	12% (22/181)
Cystectomy data	Duplisea et al (CUAJ 2018)	Booth et al (Urol Oncol 2018)
Years	2006–2014	1994–2013
Location	U.S.	Ontario, Canada
NACT	10% 2006 32% 2014	12% 2009 27% 2013
ACT	Not reported	20% (2009–2013)

they referred patients for NAC), 46% felt it was their responsibility to select which patients are eligible for chemotherapy and only refer those patients.

It is clear that not all patients are eligible for NAC. In the metastatic setting, a consensus definition of “cisplatin-ineligible” patients includes: 1) Eastern Cooperative Oncology Group (ECOG) performance status 2 or greater; or 2) creatinine clearance <60 ml/min; or 3) grade 2 or greater hearing loss; 4) grade 2 or greater neuropathy; or 5) New York Heart Association Class III heart failure.<sup>21</sup> If patients are not fit to receive cisplatin-based NAC, they should proceed directly to cystectomy.<sup>13,14</sup> There is no good evidence to support the substitution of carboplatin in cisplatin-ineligible patients. While some patients may be ineligible for NAC, and some patients may decline NAC, the position that our group and others have proposed is that each patient with MIBC should be seen by MO in consultation (and potentially by a radiation oncology as well to discuss bladder-sparing options), or at least be discussed at a multidisciplinary cancer conference. This is a standing recommendation endorsed by Bladder Cancer Canada, the Canadian Urologic Oncology Group, and the Canadian Urological Association.<sup>14</sup>

It is worth mentioning one final recent threat to the uptake of perioperative chemotherapy for MIBC: immunotherapy. Recent uncontrolled, non-randomized, single-arm trials with unvalidated surrogate clinical endpoints (e.g., pathological complete response rate) have explored the use of neoadjuvant immunotherapy for MIBC.<sup>22</sup> The PURE-01 trial was an open-label, single-arm, phase 2 study of pembrolizumab as neoadjuvant therapy for 50 patients with MIBC (cT2–3bN0M0). Patients were eligible to enroll regardless of their cisplatin eligibility; 92% (46/50) of patients were determined to be eligible for cisplatin-based chemotherapy. This study reported a pathological complete response rate of 42% (confidence

interval [CI] 28.2–56.8%). For reference, the phase 3 randomized SWOG-8710 trial of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), which included patients with T4a disease, reported pathological complete response rates of 38%. Until Level 1 evidence has shown that neoadjuvant immunotherapy confers a survival benefit, standard of care should remain cisplatin-based chemotherapy.

What is the way forward to improve the rate of perioperative chemotherapy use for MIBC? First, we must continue to measure and report proportions of patients who have a preoperative referral to MO or have discussions at multidisciplinary case conferences. There is no reason why this number cannot approach 100%. Second, we must establish clear benchmarks for perioperative chemotherapy utilization rates.<sup>23</sup> These will act as guideposts so that we can compare our observed to expected performance. Third, and most importantly, we need to fundamentally change the way we approach this problem. Investigators in many countries (including ourselves) have been describing this problem for the past decade. It is time to move beyond simply describing gaps in care and instead devote efforts to close the gap between evidence and practice. This will require multidisciplinary efforts in knowledge translation to understand barriers and enablers from the provider’s perspective, as well as a better understanding of patient preference. One tangible and achievable target that should be the first step in this effort is to ensure that all patients with MIBC receive multidisciplinary input before cystectomy.

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